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09/863,976	05/23/2001	Farzan Rastinejad	PC10228B	1819

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/863,976	RASTINEJAD ET AL.	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-103* is/are pending in the application.

4a) Of the above claim(s) *56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Remarks filed 1 June 2007 have been acknowledged and made of record.

Applicants argue that the In re Wands opinion outlined relevant considerations for enablement, but disagree with the analysis and rejection. Applicants disclose that the current invention is drawn to drug discovery. Further, applicants argue that it is unclear what the examiner is requiring to be predictable in order to practice the invention.

However, applicants' remarks are not found persuasive.

Applicants' invention is drawn to halting or repression of tumor growth. This would constitute an association with the treatment of cancer. The screening methods as disclosed are essentially directed to methods for determining via the combination of a compound to a polypeptide or fragment thereof. A restoration or stabilization occurs resulting in a functional conformation, which halts or represses tumor growth *in vivo*.

Applicants have broadly defined the claimed screening methods as disclosed in the instant claims.

Additionally, there is no specific disclosure of the positive and/or negative results connected to the actual treatment of cancer.

Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Objection

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 36, line 29 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejection(s) – 35 USC§ 112, 1ST paragraph New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58, 63, 65, 71, 84, 87, 88, 91, 92, 94-97, and 100-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instant claim 63 cites the method of claim 58 that is performed in a cell-free environment. Applicants' Remarks disclose that pending claim 63 correlates with pages 35-36 of the instant specification. In consideration of the cited pages, the claim limitation of "a cell-free environment" is not readily or adequately elucidated within the embodiments of instant pages 35-36. One of ordinary skill in the art would not be so inclined as to recognize the said limitation of "a cell-free environment" based on the disclosure of said pages *supra.* In accordance, the limitation, "a cell-free environment" is not defined, described and/or explained in the instant

claims or specification in such a way as to convey relevance commensurate with claimed invention.

Instant claims 65, 71, 84, 87, 88, 91,92, 94-97, and 100-103 cite, wherein said polypeptide comprises the p53, p63, or p73 DNA binding domain and the method [...], wherein said polypeptide comprises the p53 DNA binding domain. Applicants' Remarks disclose that pending claim 84 correlates with previous claims 34 and 37 and that pending claim 87 correlates with previous claim 34. Respectively, both claims cite the method [...] wherein said protein comprises the DNA binding domain of said p53 protein without the entire N and C terminal domains and a method [...] wherein said protein of the p53 family is selected from the group consisting of p53, p63, and p73. The breadth of instant claim 84 has become broader in scope of invention based on applicants' amendment to instant claim 84. The absence of the claim limitation *"without the entire N and C terminal domains"* or a modification thereof disclosed within pending claim 84 makes it broad in comparison to alleged correlating claims 34 and 37 (with specific emphasis on instant claim 34).

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 57-62, 64,65, 68, 69, 72, 74, 75, 77, 79-95, 100, and 101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Welch et al. (USPN 5,900,360) (already of record) in view of Das et al. (already of record).

Welch et al. fundamentally teach methods of improving phenotypic defects that are caused by conformationally defective target proteins. The methods of the invention comprise exposing a cell that expresses a conformationally defective target protein with an amount of a protein stabilizing agent that is effective to improve the phenotypic defect. Nonlimiting examples of protein stabilizing agents include dimethylsulfoxide (DMSO), deuterated water, trimethylamine N-oxide (TMAO). Nonlimiting examples of defective target proteins to be treated include the cystic fibrosis transmembrane conductance regulator (CFTR) protein and prion proteins. In one embodiment, the invention provides methods for detecting protein stabilizing agents. In another embodiment, the invention provides methods for detecting cells and pathological conditions caused by improper folding and protein processing (abstract only).

Welch et al. teach cell lines expressing **temperature sensitive mutants** of: the tumor suppressor protein p53; the viral oncogene protein pp60.sup.src ; or an ubiquitin activating

enzyme E1, were incubated at the nonpermissive temperature (39.5.degree. C.) in the presence of glycerol, trimethylamine N-oxide or deuterated water. In each case, the cells now exhibited phenotypes similar to that observed when the cells were incubated at the permissive temperature (32.5.degree. C.), indicative that the particular protein folding defect had been corrected. See also Brown et al., 1997, J. Clin. Invest. 99:1432-1444. Thus, protein stabilizing agents are effective in vivo for correcting protein folding abnormalities (column 4, lines 15-26).

Also, Welch et al. teach protein stabilizing agents that are not specifically disclosed herein may be routinely identified by any of the following model methods. As a threshold test, candidate protein stabilizing agents can be identified by their ability to stabilize ***in vitro*** certain physical (e.g., reduce aggregation in response to chemical or thermal treatment) and functional (e.g., retain enzymatic activity in response to chemical or thermal treatment) properties of either wild type or conformationally defective proteins. Candidate agents can then be tested in cellular systems such as the mutant CFTR and prion protein expressing cell lines described below. These assays are also useful to determine the relative potency of different protein stabilizing agents, by comparing the ability of a putative protein stabilizing agent to stabilize a biologically active conformation or to induce a conformationally defective protein to become more like the wild type protein, relative to a known well characterized standard protein stabilizing agent (e.g., glycerol) (column 7, lines 66 and 67); column 8, lines 1-15).

Further, Welch et al. teach one method of defining whether a test substance is a "protein stabilizing agent" is to determine its ability to stabilize a protein in vitro to aggregation induced by thermal treatment, changes in pH, or the addition of protein chaotropes (e.g., urea, guanidinium chloride). The assay is performed, for example, by (1) incubating 0.1 to 10 mg/ml

of a test wild type protein in the presence or absence of preselected concentrations (**ranging from about 0.1.mu.M to about 1 M**) of a test compound, (2) subjecting the test protein to denaturing conditions, (3) **measuring the alterations, if any, in the test protein's physical properties (e.g., light absorbance, aggregation, solubility in a specific solvent, .alpha.-helix or .beta. sheet content, shape) in the presence or absence of the test compound, and (4) assessing the ability of the test protein to retain wild type behavior and physical properties in the presence and absence of the test substance**. For example, the physical property may be a tendency to aggregate in a given solution. Aggregation may be measured by light scattering, velocity sedimentation, or other known techniques. Conditions which cause aggregation include thermal treatment (incubation at 10-70.degree. C.), pH treatment (e.g., incubation at a pH selected from pH 2-10), or the addition of protein chaotropes (e.g., 1-8 M urea or guanidinium chloride). Many others are known in the art and are encompassed by the invention. Protein stabilizing agents are those test substances which reverse, reduce, or prevent the effects (e.g., denaturation, aggregation) of the protein denaturing agent (e.g., acid, detergent) or treatment (pH, temperature)(column 8, lines 17-45).

Accordingly, Welch et al. teach a cell line that expresses a phenotypic defect associated with the gene product of a homologous or heterologous gene is tested for the presence of a measurable biological activity, such as enzymatic activity, normally associated with the wild type protein but not with the conformationally defective target protein. For example, this activity may be temperature-sensitive. A temperature-sensitive protein or activity is one that is less active than the wild type protein or activity at a particular defined ("non-permissive") range of temperatures, but behaves more like the wild type at a second defined ("permissive") range of

temperatures. For example, temperature-sensitive proteins in **mammalian cells** are often active under 30.degree. C. the "permissive" temperature), but are relatively inactive at **37.degree. C.** (the "non-permissive"temperature). A protein stabilizing agent is a test substance that, when present in a defined concentration, causes the enzyme to retain or acquire at least 10% of the **wild type activity** at the non-permissive temperature (column 9, lines 23-41).

Further, Welch et al. teach a number of cell types [which] are useful for the practice of this invention and are readily available. These include cells of fibroblastic or epithelial origin which do not express endogenous CFTR. These cells may be of rodent, feline, canine, bovine, equine, ovine, nonhuman primate, or **human origin**. The cells may be primary isolates, immortalized, or genetically modified using techniques known to those of skill in the art.

Still further, Welch et al. teach monoclonal antibodies, missense mutations, wild-type and mutant forms of p53, and fluorescent micrographs (i.e., fluorescent labeling) (column 16, line 6; column 25, lines 1 and 41-56; column 29, line 34).

Claim 1 of said patented reference *supra* discloses a screening method for detecting a concentration of a test protein stabilizing agent which is effective to improve a phenotypic defect that is caused by a conformationally defective protein, comprising the steps of contacting a range of concentrations of a test substance with a cell that contains a conformationally defective target protein wherein said conformationally defective protein causes a phenotypic defect, and determining a concentration of said test substance which is effective to improve a conformational defect of said conformationally defective protein and improve the phenotypic defect of the cell;[...] (column 32, lines 35-48).

Welch et al. does not teach a cell-free environment according to instant claim 63.

Welch does not teach a solid phase surface, the anchoring of a polypeptide, an antibody-polypeptide complex, mAb 1620 or mAb 240 specifically, an epitope of p53, residue positions, measurements of the effect on polypeptide conformation via chromatography, spectroscopy, absorption, etc., a candidate compound that fits the hypothesis, transcriptional activation domain or oligomerization domain as disclosed in instant claims 66, 67, 70, 71,73,76,78, 96-99, 102 and 103.

However, Das et al. teach the use of fluorescence spectroscopy to determine the conformation of destabilized protein bound to the chaperone alpha-crystallin, which is known to suppress the aggregation of damaged proteins. (Please see abstract only).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Welch et al. by using spectroscopy to determine the stabilized or functional conformation of the mutant p53 protein bound to the stabilizing agents because one of ordinary skill in the art would reasonably expect spectroscopy to be equally effective in studying the interaction between the mutant p53 protein and stabilizing agent of Welch et al. Such a modification would have been motivated by the reasonable expectation of determining the conformational aspects of the bound mutant protein and agent thereby accurately identifying the non-peptide compound that may be useful in treating cancer.

Concerning the claims drawn to the use of a human p53 protein and the use of various mutant proteins, one of ordinary skill in the art would reasonably expect these specific types of mutant p53 proteins as well as a p53 protein from a human to be equally useful in the claimed

identification method, especially since the identified non-peptide compounds may be eventually useful in treating cancer in humans.

Additional screening of the identified compound for anti-tumor activity using cell lines or tumor cells is an art-recognized, result-effective variable and it would have been obvious to one of ordinary skill in the art to modify it in the method of Welch et al.

Finally, the use of antibodies as a linking agent to a solid support as well as the use of radioisotope or fluorescent labels are conventional and well within the capability of the skilled artisan.

Claim Rejection(s) – 35 USC§ 112, 1ST paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The alleged invention is deficient regarding the treatment of cancer. Accordingly, the instant claims are absent of any treatment specifically for cancer. There remains a lack of enablement drawn to the absence of an ultimate usage of the claimed invention.

As stated in MPEP 2164.01(a), " There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue."

In re Wands, set forth the following eight factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, 1ST paragraph:

1. The nature of the invention;
2. The state of the prior art;
3. The predictability or lack thereof in the art;
4. The amount of direction or guidance present;
5. The presence or absence of working examples;
6. The breadth of the claims;
7. The quantity of experimentation needed; and
8. The level of the skill in the art.

The state of the prior art and the predictability or lack thereof in the art

The state of the art, pharmacology, involves screening *in vitro* and *in vivo* in order to determine which compounds exhibit pharmacological activities. There is no reasonable predictability, even in view of the seemingly high level of skill in the art.

Accordingly, the issue of unpredictability is directed to the absence of any disclosure drawn to efficacy and /or the actual treatment of cancer. Likewise, the instant claims and

specification do not adequately elucidate the measure, order, or degree of tightness/connectivity in the binding of p53. Further, the specification and claims are absent of embodiments or disclosures as to what concentrations or conditions of screening assays of current invention result in binding and would be predictive of cancer treatment.

The amount of direction or guidance present

The amount of direction or guidance present in instant specification and instant claim set is deficient in light of the nature of the alleged invention (treatments for cancer).

The breadth of the claims, quantity of experimentation

The breadth of the claims is broad including variant factors, which would require continued exhaustive experimentation. The level of the skill in the art requires high expertise due to the nature of the invention (treatment of cancer).

The instant specification is absent of any specific explanations and/or description as to how cancer may be treated in accordance to the objectives of claimed invention. The disclosures within the instant specification are directed to what the skilled artisan may be inclined to recognize as "a lab curiosity" with no substantial support or adequate explanation commensurate in scope with the claimed objective, i.e., treatment of cancer.

Further, the embodiments drawn to aspects of binding are not sufficiently clear in view of the said objective of the claimed invention.

Again, as stated in MPEP 2164.01(a), " There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue."

Subject claim 57 is not enabled due to a lack of explanation in view of the ultimate use as disclosed in the instant invention directed to the treatment of cancer.

Furthermore, in the instant specification (page 49, lines 17-24), applicants' disclose that nature of the compound interaction with p53 may not involve tight binding to the native protein structure. A strong interaction with a **small** subset of the protein molecules that are in the transition state may function to block further deviation from the active conformation or facilitate reversion to the native conformation. The above statement disclosed suggests the need for on-going experimentation.

Conclusion

Claims 57-103 stand rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

Ardin H Marschel 12/12/07
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SUPERVISORY PATENT EXAMINER